The scientific concept to establish 'causation' for multifactorial diseases

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Scientific proof for causality

A specific exposure of a person is

necessary and ***sufficient***

to result in a specific disease.

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Multifactorial diseases

- More than one exposure can result in the disease
- Common mechanism
- Exposure to one risk factor may not result in disease [does this belong here?]

[Risk factors for lung cancer and CVD, emphysema]

[Scheme of lung cancer mechanism]

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Concepts

- General causation
  - Refers to a population with a common exposure and common disease
  - Based on population statistics
- Specific causation
  - Refers to a specific situation of a person with a specific and an at least assumed specific exposure
  - Based on a medical/biochemical diagnosis

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Method to establish General Causation

- Use of guidelines
  - US Surgeon Generals' Report 1964
  - Bradford-Hill (1965)
- Use of opinion
  - Epidemiology only (e.g. US public health community members)
  - Epidemiology + controlled laboratory experiments (US Surgeon Generals' Report 1964)
  - Epidemiology + biological plausibility (e.g. US EPA 1992?)
  - Epidemiology + mechanism + responsible chemical(s)
  -

Epidemiology + # intervention

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US Surgeon General guidelines 1964

- Strength of statistical association
- Consistency
- Dose-response
- Temporality
- Specificity
- Coherence

- The report claims that 5 out of these 6 criteria are met for the relationship between cigarette smoke and lung cancer

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Bradford-Hill (1965)

- Addition to SG-64 criteria: Cessation results in decline

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Epidemiology

- Smoking consistently found to be one of the strongest risk factors for lung cancer (e.g. Wynder and Graham, 1950; Doll and Hill, 1950)
- Dose-response relation established (e.g. Wynder 1957)
- Cessation results in reduction of population risk (e.g. ...)

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Controlled laboratory experiments

- Mouse skin painting (e.g. Wynder 1953)
- 'Traditional' rodent inhalation (e.g. Kuori and Henry, [hamster], Dalham, Lovelace, reviewed by Coggins 1998?)
- Dog inhalation (Auerbach)
- 'New' mouse inhalation (A/J mouse; Witschi 19..)

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Biological plausibility claims

- Cigarette smoke contains substances classified as human and/or animals carcinogens
- Tumorigenicity of cigarette smoke condensates in mouse skin painting assay
- Mutagenicity of cigarette smoke condensate in Salmonella assay (Ames assay)

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Detailed molecular or genetic mechanism(s) linking smoking and cancer

- New techniques (80s) suggest a link between somatic mutations in critical DNA sites and the development of certain cancers
  - Identification of human oncogenes (e.g. Shimizu 1983)
  - Approx 30% of human lung tumors contain tumorigenic forms of ras, myc, or erb
  - Approx 50% of human lung tumors contain mutated tumor suppressor genes such as p53 (Hollstein 1991)
  - Not all cells with mutated p53 grow as cancer cells
  - Lung tumor p53 reported to contain 3 'hotspots'
- TS contains agents with the potential to initiate such mutations
  - BPDE reported to form adducts with p53 hotspots (Denissenko, 1996)

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Status

No one has yet succeeded in providing that any particular compound or collection of compounds in TS plays a necessary or sufficient role in causing lung cancer.

Nor can we identify with certainty any particular genetic or chromosomal alteration that necessarily and sufficiently accounts for the conversion of normal tissue growth to cancer

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PM position

[cite from website]

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